

## Common and unique network basis for externally and internally driven flexibility in cognition: From a developmental perspective

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### ABSTRACT

Flexibility is a hallmark of cognitive control and can be driven externally and internally, corresponding to reactive and spontaneous flexibility. However, the convergence and divergence between these two types of flexibility and their underlying neural basis during development remain largely unknown. In this study, we aimed to determine the common and unique networks for reactive and spontaneous flexibility as a function of age and sex, leveraging both cross-sectional and longitudinal resting-state functional magnetic resonance imaging datasets with different temporal resolutions ( $N = 249$ , 6–35 years old). Functional connectivity strength and nodal flexibility, derived from static and dynamic frameworks respectively, were utilized. We found similar quadratic effects of age on reactive and spontaneous flexibility, which were mediated by the functional connectivity strength and nodal flexibility of the frontoparietal network. Divergence was observed, with the nodal flexibility of the ventral attention network at the baseline visit uniquely predicting the increase in reactive flexibility 24–30 months later, while the nodal flexibility or functional connectivity strength of the dorsal attention network could specifically predict the increase in spontaneous flexibility. Sex differences were found in tasks measuring reactive and spontaneous flexibility simultaneously, which were moderated by the nodal flexibility of the dorsal attention network. This study advances our understanding of distinct types of flexibility in cognition and their underlying mechanisms throughout developmental stages. Our findings also suggest the importance of studying specific types of cognitive flexibility abnormalities in developmental neuropsychiatric disorders.

### 1. Introduction

Cognitive and behavioral flexibility, which allows humans to develop complex and diverse functions, is critical for cognitive and socio-emotional development (Diamond, 2016). The triggers of flexible cognitive control can be external or internal. Examples of externally driven flexibility include quickly adapting to changing situations, while examples of internally driven flexibility include thinking from different perspectives (Diamond, 2013). Accordingly, two types of cognitive flexibility have been proposed by Eslinger and Grattan: reactive flexibility refers to quick and adaptive adjustments to environmental changes, and spontaneous flexibility refers to generating various ideas for a given topic or question (Eslinger and Grattan, 1993). While both types of cognitive flexibility involve flexible cognitive control, reactive flexibility requires more reactive control to quickly respond to changing

environmental demands and conflicts (Kiesel et al., 2010), and spontaneous flexibility entails more proactive control to plan and voluntarily adjust strategies without explicit prompts (Diamond, 2013; Eslinger and Grattan, 1993; Weiss et al., 2006). Developmental neuroscience research on different types of flexibility could reveal how the brain develops to meet various demands from the external and internal world.

A number of experimental tasks have been used to assess cognitive flexibility in developmental studies, including ideational fluency, verbal fluency, design fluency, task-switching, and set-shifting (Diamond, 2013; Kupis and Uddin, 2023). In behavioral studies, the fluency tasks are considered to measure spontaneous flexibility, while the task-switching, wisconsin card sorting test, and trail-making test (TMT) are assumed to measure reactive flexibility (Arán Filippetti and Krumm, 2020; Ebersbach and Hagedorn, 2011; Parkin and Lawrence, 1994; Zmigrod et al., 2019). The different types of cognitive flexibility

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consistently show a non-linear developmental trajectory: increasing significantly in childhood and adolescence and reaching a plateau in early adulthood (Cepeda et al., 2001; Kupis and Uddin, 2023; Tervo-Clemmens et al., 2023). However, previous studies often used single tasks to measure each type of cognitive flexibility, and thus the findings may be influenced by task selection (Deák and Wiseheart, 2015; Yeo et al., 2015). It is therefore necessary to explore developmental changes in each type of cognitive flexibility by incorporating multiple tasks.

In terms of neural mechanisms, task-based functional magnetic resonance imaging (fMRI) studies have shown the involvement of several functional networks in different types of cognitive flexibility in children, adolescents, and adults. Specifically, when performing reactive flexibility tasks, regions in the frontoparietal (FPN), dorsal attention (DAN), ventral attention (VAN), salience (SN), and subcortical (SUB) networks, have been consistently recruited in adults and children (Dajani and Uddin, 2015; Kim et al., 2012; Kupis and Uddin, 2023). Regarding spontaneous flexibility, brain regions in the default mode network (DMN), FPN, VAN, and DAN are activated in adults and children when performing verbal fluency tasks (Gaillard et al., 2000; Li et al., 2017; Wagner et al., 2014). Moreover, functional connectivity between FPN and VAN and between FPN and DMN has been documented to increase during the performance of reactive flexibility (Yin et al., 2018) and spontaneous flexibility tasks (Arrigo et al., 2024), respectively. However, task fMRI findings may depend on specific task paradigms, and most neuroimaging studies have used only a single task.

In the absence of any overt task, resting-state fMRI is often used to describe intrinsic functional networks (Fox and Raichle, 2007; Yeo et al., 2011), which are considered functional fingerprints that can predict an individual's cognitive performance (Baldassarre et al., 2012; Finn et al., 2015; Van Den Heuvel and Pol, 2010). Resting-state functional connectivity of the FPN, VAN, and DMN has been related to the performance of reactive flexibility tasks in adults and children (Müller et al., 2015; Thomas et al., 2023; Yin et al., 2015). Functional connectivity within the FPN or between the FPN and DMN has been linked to the performance of spontaneous flexibility tasks in children and adults (Gordon et al., 2011; Shi et al., 2018). In particular, recent studies have revealed the relevance of dynamic reconfigurations of intrinsic functional networks to cognitive flexibility (Chen et al., 2016; Kupis et al., 2021; Nomi et al., 2017). Specifically, dynamic intrinsic functional connectivity between the FPN and DMN is associated with reactive flexibility in children, adolescents, and adults (Douw et al., 2016; Luo et al., 2023). In addition, a prior study has demonstrated a significant association between the temporal flexibility of the SN and the performance of reactive flexibility tasks in young adults (Chen et al., 2016). Several studies have also investigated the associations between spatiotemporal dynamics of brain networks and reactive flexibility (Kupis et al., 2021; Lee et al., 2022) or spontaneous flexibility (Boon et al., 2020; Engels et al., 2018) in old adults. Unfortunately, few studies have focused on the brain dynamics underlying different types of cognitive flexibility during development.

Cognitive flexibility may exhibit sex differences due to the distinctions in the developmental pace of brain structure and function between males and females (Lenroot and Giedd, 2010; Ruigrok et al., 2014). From childhood to young adulthood, males and females differ in structural and functional connectivity, task-related activation, and temporal dynamics of brain activity (Cai et al., 2020; Ingalhalikar et al., 2014; Shanmugan et al., 2022). For example, males and females prefer to recruit the parietal and prefrontal cortices, respectively, in cognitive control (Christakou et al., 2009). In the domain of cognitive flexibility, females have been observed better performance than males in both reactive and spontaneous flexibility tasks in childhood and adolescence (Anderson et al., 2001; Anokhin et al., 2010; Kalkut et al., 2009). However, inconsistent findings on sex differences were observed in these tasks during development (Van der Elst et al., 2011; Welsh et al., 1991). It is not clear yet whether the overall sex differences exist for each type of cognitive flexibility, and how the brain regulates the effects of sex.

Previous task and resting-state fMRI studies have mainly focused on one type of flexibility, and few studies have investigated the neural basis of both reactive and spontaneous flexibility during development. Therefore, this study aimed to explore developmental changes and sex differences in different types of cognitive flexibility (Fig. 1A) and their functional network basis, using both static and dynamic functional brain metrics (Fig. 1B) and both cross-sectional and longitudinal behavioral and resting-state fMRI data (Fig. 1C). Based on the cross-sectional dataset, we investigated age and sex effects on different types of cognitive flexibility and which functional networks mediated or moderated the relationship between age or sex and cognitive flexibility (Baum et al., 2017; Satterthwaite et al., 2013) (Fig. 1D). The longitudinal dataset was mainly used to test whether baseline brain measures could predict the increase in cognitive flexibility over the course of development (Fig. 1E). We expected reactive and spontaneous flexibility to show similar developmental trajectories, although they may be supported by both common and unique functional brain networks. It is conceivable that the FPN would be the common network for supporting cognitive control involved in both types of cognitive flexibility. Moreover, we hypothesized that there would be sex effects on cognitive flexibility that might be moderated by certain higher-order brain networks, such as the attention networks and the FPN, because of the different importance of the prefrontal and parietal cortices for males and females (Christakou et al., 2009; Zaidi, 2010).

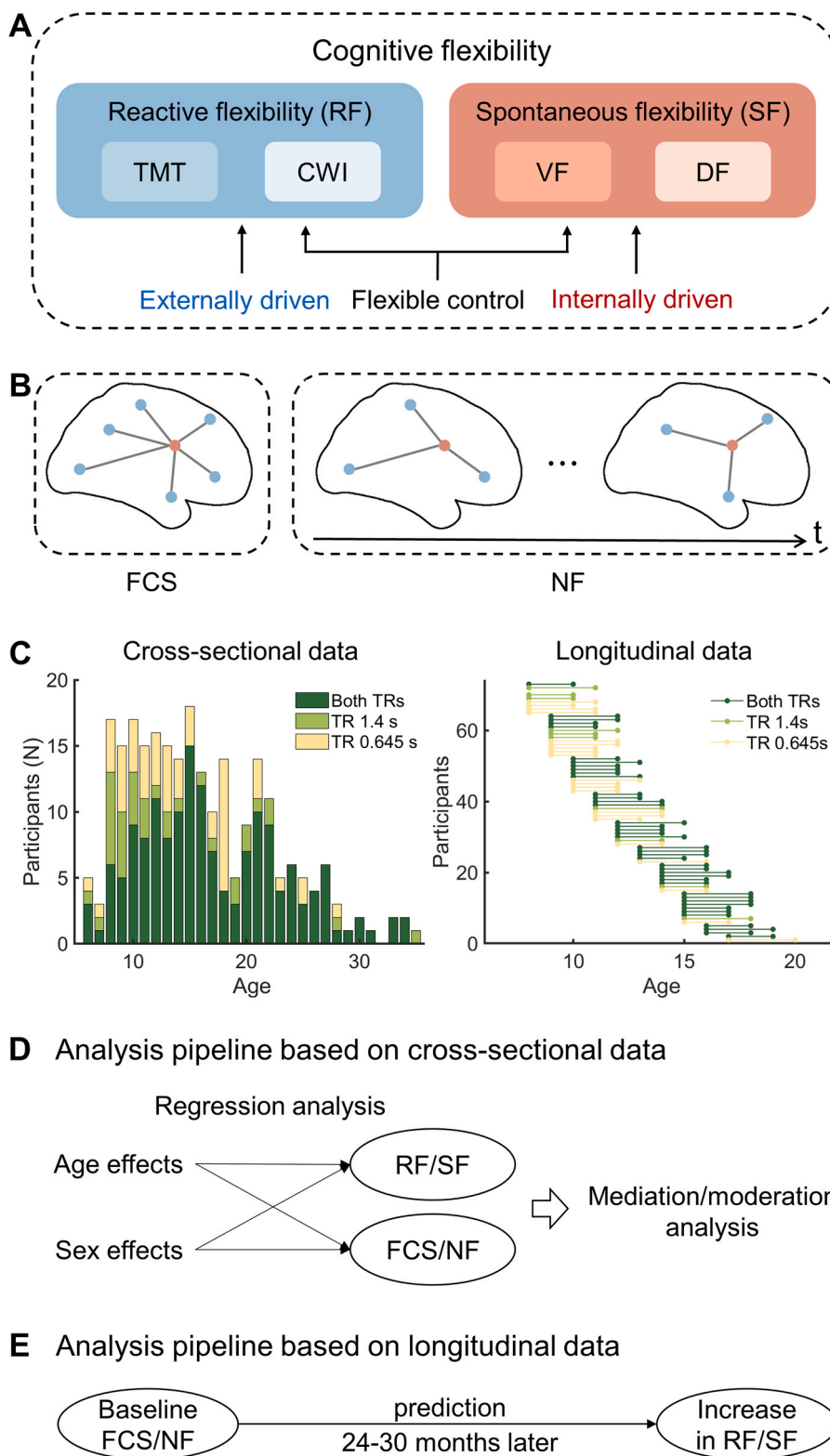
Furthermore, the vast majority of fMRI studies used only one repetition time (TR) of about 2 s, especially before the emergence of the multi-band technique (TR ~ 0.5 s). While the consistency in functional measurements has been observed at different temporal resolutions (Qin et al., 2015; Shakil et al., 2016), accumulating evidence indicates that higher temporal resolution may confer additional benefits (Chen et al., 2015; Demetriou et al., 2018; Preibisch et al., 2015). For instance, a recent study showed that brain dynamics calculated from the data with higher temporal resolution were more sensitive to age-related changes (Nomi, Bolt, et al., 2017). Therefore, we used different TRs (1.4 s and 0.645 s) to investigate the potential effects of temporal resolution on static/dynamic functional metrics and their relationship to age and cognitive flexibility. We expected that the dynamic measure based on the fast TR (0.645 s) may be more sensitive to individual differences in cognitive flexibility.

## 2. Materials and methods

### 2.1. MRI and behavioral protocols

Behavioral data and resting-state functional MRI data were downloaded from publicly available datasets: Enhanced Nathan Kline Institute Rockland Sample (NKI-RS) (Nooner et al., 2012; Tobe et al., 2022). The NKI-RS included both a cross-sectional lifespan sample (6–85 years old) and a longitudinal developing sample (6–17 years old) of neuroimaging and behavioral data. There were 369 children and adolescents enrolled in the longitudinal sample, among whom 177 completed the follow-up assessments 24–30 months after their baseline visits. Most previous studies of functional brain development adopted only cross-sectional data and lacked longitudinal assessments, especially for functional images (Telzer et al., 2018). While cross-sectional data can characterize developmental changes across different ages, longitudinal assessments allow to track changes in individual participants and predict their subsequent performance. To provide a more comprehensive understanding of developmental changes, we used both cross-sectional and longitudinal datasets (Fig. 1C).

The resting-state fMRI data were collected at different temporal resolutions: TR equals 2.5 s, 1.4 s, and 0.645 s. Here we used the TR 1.4 s and TR 0.645 s datasets because their acquisition time is relatively long (about 10 min) compared to the TR 2.5 s dataset (5 min) and a longer time is conducive to estimating more reliable functional networks (Birn et al., 2013).



**Fig. 1.** An overview of the methodology and datasets. (A) Two types of cognitive flexibility: the TMT and CWI are considered reactive flexibility (RF) -specific tasks, whereas VF and DF are considered spontaneous flexibility (SF) -specific tasks. The common process of the two types is flexible cognitive control, and the key difference is that reactive flexibility is largely externally driven whereas spontaneous flexibility is mainly internally driven. (B) Two brain metrics are derived from temporally static and dynamic frameworks, respectively: functional connectivity strength (FCS) and nodal flexibility (NF). (C) Participants included in the final cross-sectional and longitudinal analyses in the datasets with different temporal resolutions: TR 1.4 s and TR 0.645 s. (D) Analysis pipeline based on cross-sectional data. The age and sex effects on FCS/NF and RF/SF were first examined by regression analysis. Then, mediation or moderation analysis was further performed. (E) Analysis pipeline based on longitudinal data. The increase in RF/SF after 24–30 months of follow-up was predicted by the baseline FCS/NF. TMT: trail-making test; CWI: color-word interference; VF: verbal fluency; DF: design fluency; and TR: repetition time.

## 2.2. Participants

A total of 196 (95 males) and 213 (106 males) participants aged 6–35 years were selected from the TR 1.4 s and TR 0.645 s datasets, respectively (Table 1), according to the following inclusion criteria: (1) no diagnosis or condition of psychopathology and brain injury; (2) availability of T1-weighted images and at least one session with functional images; (3) no image quality issue detected by visual inspection; (4) maximal translation of head motion < 3 mm or maximal rotation angle < 3°; (5) full-scale IQ (FIQ)  $\geq$  80. We excluded participants who had been diagnosed with psycho-psychiatric disorders because the purpose of this study was to explore the typical development of different types of cognitive flexibility as well as their network basis. The inclusion of participants aged 30 in this study was to comprehensively depict the changes in cognitive flexibility across different age groups since previous studies suggested that the performance may reach a peak between 20 and 30 years old (Cepeda et al., 2001; Kalkut et al., 2009). The number of overlapped participants in the two datasets was 160. No significant differences were found in age or behavioral assessments between the two datasets (Table 1). Only 51 and 63 participants under 18 years of age completed the follow-up assessments approximately 24–30 months after the baseline visits in the TR 1.4 s and TR 0.645 s datasets, respectively.

## 2.3. Behavioral measures of cognitive flexibility

Participants aged  $\geq$  8 years were administered the full Delis-Kaplan Executive Function System (D-KEFS) battery (Delis et al., 2001). Among the tests, the TMT, color-word interference (CWI), verbal fluency (VF), and design fluency (DF) were selected to measure cognitive flexibility.

In the TMT task, participants were first instructed to make connections between numbers and between letters separately by sequence and then were instructed to make connections back and forth between numbers and letters by sequence (number-letter switching).

In the CWI task, participants were required to complete subtests of four conditions: color naming, word reading, inhibition (naming the ink color of a color word, like the Stroop test), and switching between naming the color of the ink and reading the color word (inhibition/switching).

In the VF task, participants were first instructed to produce non-repetitive words that begin with a certain letter or belong to a pre-defined category (letter fluency and category fluency) and then were instructed to name words between two different categories (category switching).

**Table 1**  
Participants information and behavioral performance of cross-sectional data.

	TR 1.4 s	TR 0.645 s	<i>p</i>
N	196	213	-
Age (year)	16.74 ( $\pm$ 6.37)	16.41 ( $\pm$ 6.21)	0.33
Gender	95 M 101 F	106 M 107 F	-
Full-scale IQ	103.44 ( $\pm$ 10.73)	103.87 ( $\pm$ 11.72)	0.96
Trail-making test: switching (TMT)	79.92 ( $\pm$ 40.25)	79.66 ( $\pm$ 35.91)	0.20
Color-word interference: switching (CWI)	66.19 ( $\pm$ 21.82)	66.83 ( $\pm$ 19.17)	0.29
Verbal fluency: category fluency (VFc)	37.40 ( $\pm$ 9.17)	37.41 ( $\pm$ 9.18)	0.35
Verbal fluency: letter fluency (VFl)	32.19 ( $\pm$ 11.29)	31.58 ( $\pm$ 11.22)	0.78
Design fluency: filled dots (DF)	9.51 ( $\pm$ 3.23)	9.59 ( $\pm$ 3.35)	0.20
Verbal fluency: switching (VFS)	12.22 ( $\pm$ 2.85)	12.24 ( $\pm$ 2.80)	0.31
Design fluency: switching (DFS)	7.72 ( $\pm$ 2.78)	7.60 ( $\pm$ 2.82)	0.76

Raw scores used in each task: TMT: number-letter switching - total time to complete; CWI: inhibition/switching - total time to complete; VFc: category fluency raw; VFl: letter fluency raw; DF: filled dots; VFS: category switching raw; DFS: switching total correct; *p*: *p* values of two-sample *t*-tests between the two datasets on non-overlapping participants.

In the DF task, participants were first required to generate different geometric patterns by making connections between filled dots (fluency condition) and between empty dots separately and then were required to draw between filled and empty dots (switching condition).

For the TMT and CWI tasks, the raw scores of the total completion time in seconds under the switching conditions were used for subsequent analyses. For the VF and DF tasks, raw scores of the fluency and switching conditions were used for later analyses. According to the definitions for the two types of cognitive flexibility and the classification in previous studies (Arán Filippetti and Krumm, 2020; Ebersbach and Hagedorn, 2011; Parkin and Lawrence, 1994), the TMT and CWI were classified as reactive flexibility-specific tasks, whereas the VF and DF were classified as spontaneous flexibility-specific tasks (Fig. 1A). To note, the fluency condition of the two fluency tasks was used to assess the ability to generate nonrepetitive words or geometric patterns, which was often used to measure spontaneous flexibility (Arán Filippetti and Krumm, 2020; Ebersbach and Hagedorn, 2011). The switching condition added external constraints based on fluency tasks, for example, generating words between two categories or generating patterns between filled and empty dots back and forth, which required reactive and spontaneous flexibility simultaneously.

The z-scores of each task were obtained for cross-sectional and longitudinal datasets separately. Given that adults did not have follow-up scores, we combined the adults' baseline scores and follow-up scores of children and adolescents to calculate z-scores for the follow-up session. The reactive flexibility (RF) score was obtained by averaging the z-scores of TMT and CWI tasks (switching condition), and the spontaneous flexibility (SF) score was obtained by averaging the z-scores of VF and DF tasks (fluency condition), while the reactive and spontaneous flexibility (RSF) score was obtained by averaging the z-scores of VF and DF tasks (switching condition). Higher scores indicate better cognitive flexibility. Because the raw scores of the reactive flexibility tasks were reaction times, which were negatively correlated with task performance, we inverted the scores to ensure that all behavioral scores in later analyses were positively associated with cognitive flexibility. Outliers were defined as values that deviated from the median by more than 3 times the median absolute deviation (Leys et al., 2013) and were treated as missing values.

## 2.4. MRI data acquisition and preprocessing

Resting-state functional MRI datasets were acquired using Siemens Magnetom TrioTim MR scanner with the following pulse sequence parameters: for the TR 1.4 s dataset, TR = 1400 ms, echo time (TE) = 30 ms, flip angle = 65°, field of view (FOV) = 224  $\times$  224 mm<sup>2</sup>, 64 slices, voxel size = 2  $\times$  2  $\times$  2 mm<sup>3</sup>; for the TR 0.645 s dataset, TR = 645 ms, TE = 30 ms, flip angle = 60°, FOV = 222  $\times$  222 mm<sup>2</sup>, 40 slices, voxel size = 3  $\times$  3  $\times$  3 mm<sup>3</sup>.

Functional images were preprocessed using DPARSF (Yan et al., 2016) with the following steps: removing the first 10 time points, slice timing, motion correction, spatial normalization (resampling to 3 mm isotropic voxels) to MNI space, spatial smoothing (full width at half maximum = 6 mm), removing linear trends, temporal filtering (0.01–0.1 Hz), and regressing out nuisance variables including Friston 24 motion parameters, and global brain, white matter, and cerebrospinal signals.

## 2.5. Functional brain measures

The brain was divided into 200 cortical (Schaefer et al., 2018) and 32 subcortical regions (Tian et al., 2020) which were grouped into seven cortical networks (Yeo et al., 2011) and one subcortical network. Nodal flexibility (NF) was calculated in addition to functional connectivity strength (FCS) to measure the spatiotemporal dynamics of the brain. FCS was defined as the average strength of functional connectivity between a region and all other regions. To obtain the FCS, Pearson correlation



coefficients were calculated between the time series of each pair of brain regions, and then Fisher-z transformed as functional connectivity. Considering ambiguous biological interpretations of negative connections, negative values were set to zero before calculating FCS for each region (Cao et al., 2014).

NF was quantified as the entropy of a region's time-varying functional connectivity patterns (Yin et al., 2016, 2021). NF was obtained using the following steps: (1) regional time series was split into a series of overlapping time windows (window length [WL] = 60 s, step size = 1 TR), and we repeated subsequent analyses of mediation, prediction, and moderation using WL = 30 s and 100 s considering the potential influence of WL on the calculation of NF (Preti et al., 2017); (2) pairwise Pearson correlation coefficients of time series between two regions were calculated and then Fisher-z transformed as the functional connectivity for each window; and (3) the occurrence frequencies of the connections between a region  $i$  and other regions across all temporal windows were obtained.

$$P_i(j) = \frac{n(c_{ij})}{k \times w}, j = 1, 2, \dots, N, \text{ and } j \neq i \quad (1)$$

where  $P_i(j)$  is the normalized probabilistic connectivity distribution of region  $i$ ,  $n(c_{ij})$  is the number of connections between regions  $i$  and  $j$  reserved in all windows,  $k$  is the number of the strongest connections of a region in each window (here, the three strongest connections reserved), and  $w$  is the number of windows. A higher  $P_i(j)$  value indicates more frequent connections between  $i$  and  $j$  over time. The choice of  $k = 3$  has been justified for both humans and monkeys in our previous studies (Yin et al., 2019, 2021). (4) Finally, Shannon entropy, a measure of complexity, is applied to  $P_i(j)$  to obtain the NF of region  $i$ :

$$H_i = - \sum_{j=1}^N P_i(j) \times \log_2 P_i(j) \quad (2)$$

where  $H_i$  is the NF of region  $i$ . A higher value of  $H_i$  indicates more flexible functional connectivity patterns over time.

The FCS and NF were computed for each region and averaged for each network. Only higher-order brain networks (DAN, VAN, FPN, and DMN) and the SUB were considered because they have been observed to be correlated with different types of cognitive flexibility in previous studies (Eslinger and Grattan, 1993; Gordon et al., 2011; Kupis and Uddin, 2023). The definition and treatment of outliers were the same as in behavioral measures. We also calculated Pearson correlation coefficients of the NF and FCS across different TRs for the whole brain and every network to evaluate the consistency across different sampling rates.

## 2.6. Statistical analyses

### 2.6.1. Effects of age on cognitive flexibility

To explore the development of different types of cognitive flexibility, we estimated both linear and quadratic regression models for age effects with sex and FIQ as covariates based on cross-sectional data (Formulas 3 and 4). Considering that executive functions do not entirely overlap with IQ, prior studies emphasized the necessity of separating the contribution of general intellectual ability from executive functions (Delis et al., 2007; Kalkut et al., 2009; Roskam et al., 2014; Samuels et al., 2016). Accordingly, we used FIQ as a covariate in our main analysis. In contrast, some studies did not control for IQ (Baum et al., 2017; Kupis et al., 2021), given the shared variance between general intellectual ability and executive functions. Therefore, we also redone the analyses without controlling for FIQ.

$$CF = age + sex + FIQ \quad (3)$$

$$CF = age + age^2 + sex + FIQ \quad (4)$$

where CF refers to the RF, SF, or RSF scores. The optimal model was defined as the one with the larger adjusted R square among the two models. The significance level for the entire study was 0.05.

### 2.6.2. Effects of age on functional brain networks

To explore the development of functional brain networks, we estimated linear and quadratic regression models for age effects, with sex, FIQ, and the mean framewise displacement (FD) as the covariates for each network metric based on cross-sectional data (Formulas 5 and 6).

$$Brain\ metric = age + sex + FIQ + mFD \quad (5)$$

$$Brain\ metric = age + age^2 + sex + FIQ + mFD \quad (6)$$

### 2.6.3. Correlations between functional brain metrics and cognitive flexibility

To explore the direct correlations between functional brain metrics and different types of cognitive flexibility, we built linear regression models between them with sex and FIQ as covariates based on cross-sectional data (Formula 7).

$$CF = Brain\ metric + sex + FIQ \quad (7)$$

where CF refers to the RF, SF, or RSF scores.

### 2.6.4. Mediation models for the age-brain-behavior relationship

Considering the quadratic effects of age on cognitive flexibility, the MEDCURVE macro in SPSS was used to investigate the instantaneous mediating effects of the brain metrics based on cross-sectional data. The MEDCURVE macro was proposed to quantify instantaneous indirect effects when the relationships between variables were nonlinear (Hayes and Preacher, 2010). Instantaneous indirect effects were reported when the X value was set to three points (-1 standard deviation [SD], mean, and +1 SD, here is 11, 17, and 23 years old of age), and the 95 % confidence interval was obtained by bias-corrected bootstrapping 5000 times in the MEDCURVE. The quadratic effect was selected for the regression of cognitive flexibility on age, and the linear or quadratic effect was selected for the regression of brain metrics on age, according to the optimal model in Formulas 5 and 6. A linear effect was selected for assessing the regression of cognitive flexibility on the brain metrics. Sex and FIQ were used as covariates in the mediation model.

### 2.6.5. Prediction models for cognitive flexibility

Longitudinal behavioral data of children and adolescents were used only for predictive analysis. Paired  $t$ -tests were first performed on the RF, SF, and RSF scores between the baseline and follow-up visits for children and adolescents. To test whether the baseline functional brain metrics could predict the increment of cognitive flexibility at 24–30 months, multiple linear regression analyses were performed. The dependent variable was the difference in behavioral scores between the baseline and follow-up visits, the predictor was the metric of each brain network, and the covariates were age and the behavioral scores at the baseline (Formula 8). We included the baseline age as a covariate to reduce the potential influence of the large age range in the longitudinal sample. We also built a model to predict the follow-up scores using the brain metric at the baseline, while controlling for age and scores at the baseline. We supposed the results were very similar between the two models.

$$\Delta CF = brain\ network_{BAS} + age_{BAS} + CF_{BAS} \quad (8)$$

where CF refers to the RF, SF, or RSF scores, and BAS is the baseline.

Considering that increased cognitive flexibility during development may include general expectations of functioning development and superior improvement over time, we also redid the predictive analyses using the age-corrected standard scores provided by the NKI group.

2.6.6. Effects of sex on cognitive flexibility and functional brain networks

To investigate the sex differences in different types of cognitive flexibility, we further examined the significance of the sex term in the optimal model (Formulas 3 or 4) and then assessed the interactions between age or age<sup>2</sup> and sex (Formulas 9 and 10):

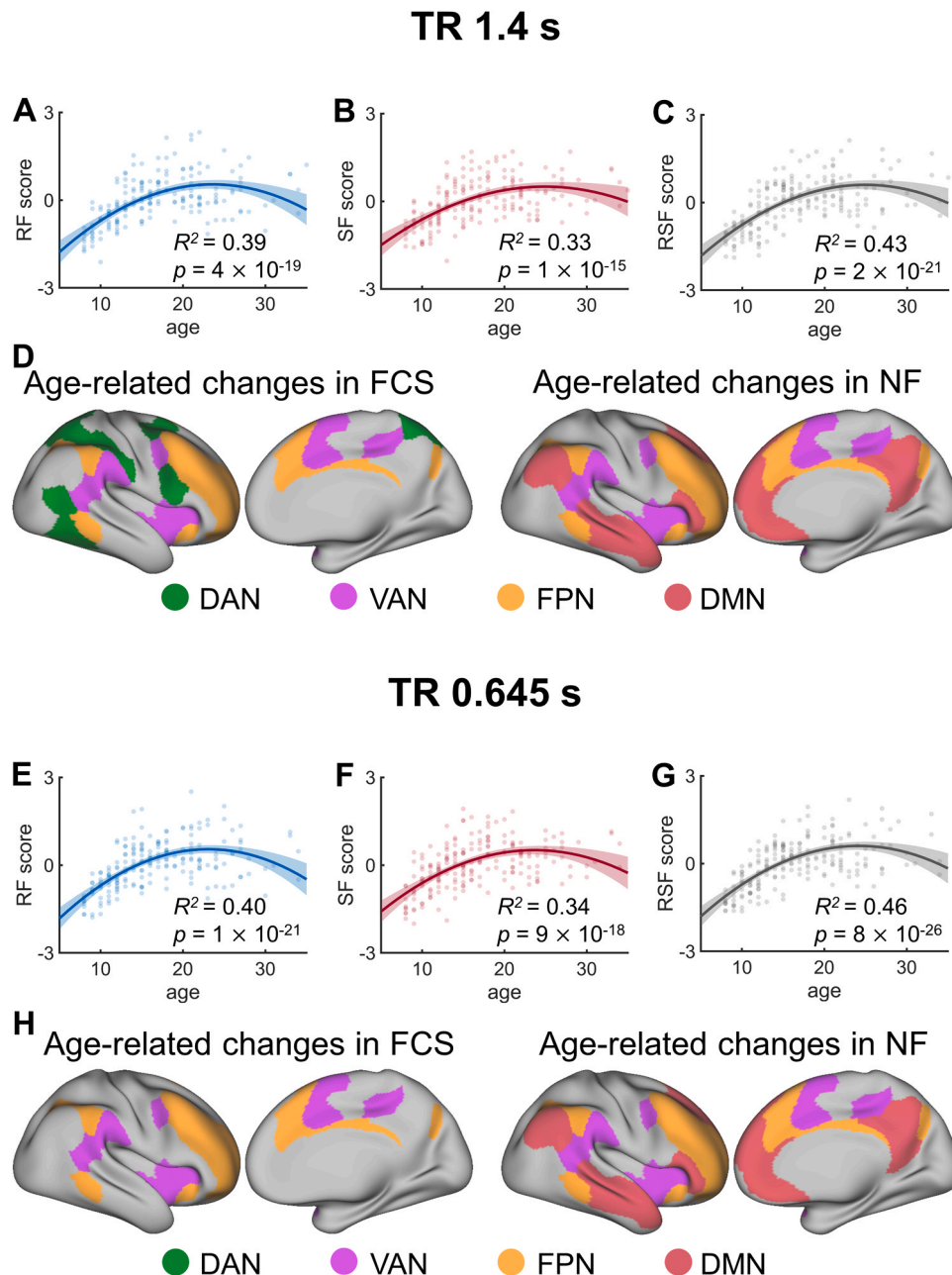
$$CF = age + sex + age \times sex + FIQ \tag{9}$$

$$CF = age + sex + age \times sex + age^2 \times sex + FIQ \tag{10}$$

where CF refers to the RF, SF, or RSF scores. The effects of sex on functional brain metrics were also examined using Formulas 5 and 6.

2.6.7. Moderation models for the sex-brain-behavior relationship

To explore the influence of brain networks on the sex effect on cognitive flexibility, moderating effects were examined using the PROCESS macro in SPSS (Hayes, 2012) based on cross-sectional data, where sex was used as an independent variable, the behavioral score was a dependent variable, each metric of the functional brain network was the moderator, and age and FIQ were the covariates.



**Fig. 2.** Effects of age on different types of cognitive flexibility and high-order brain networks. In the TR 1.4 s dataset, quadratic effects of age are observed on the RF (A), SF (B), and RSF (C) scores; (D) age-related changes are identified in the FCS of the DAN, VAN, and FPN as well as in the NF of the VAN, FPN, and DMN. In the TR 0.645 s dataset, quadratic effects of age are observed on the RF (E), SF (F), and RSF (G) scores; (H) age-related changes are identified in the FCS of the VAN and FPN as well as in the NF of the VAN, FPN, and DMN. RF: reactive flexibility; SF: spontaneous flexibility; RSF: reactive and spontaneous flexibility;  $R^2$ : adjusted  $R$  square;  $p$ : the original  $p$  of the regression model; 95 % confidence interval is highlighted in light color; DAN: dorsal attention network; VAN: salience/ventral attention network; FPN: fronto-parietal network; DMN: default mode network; FCS: functional connectivity strength; and NF: nodal flexibility.

### 3. Results

#### 3.1. Development of cognitive flexibility

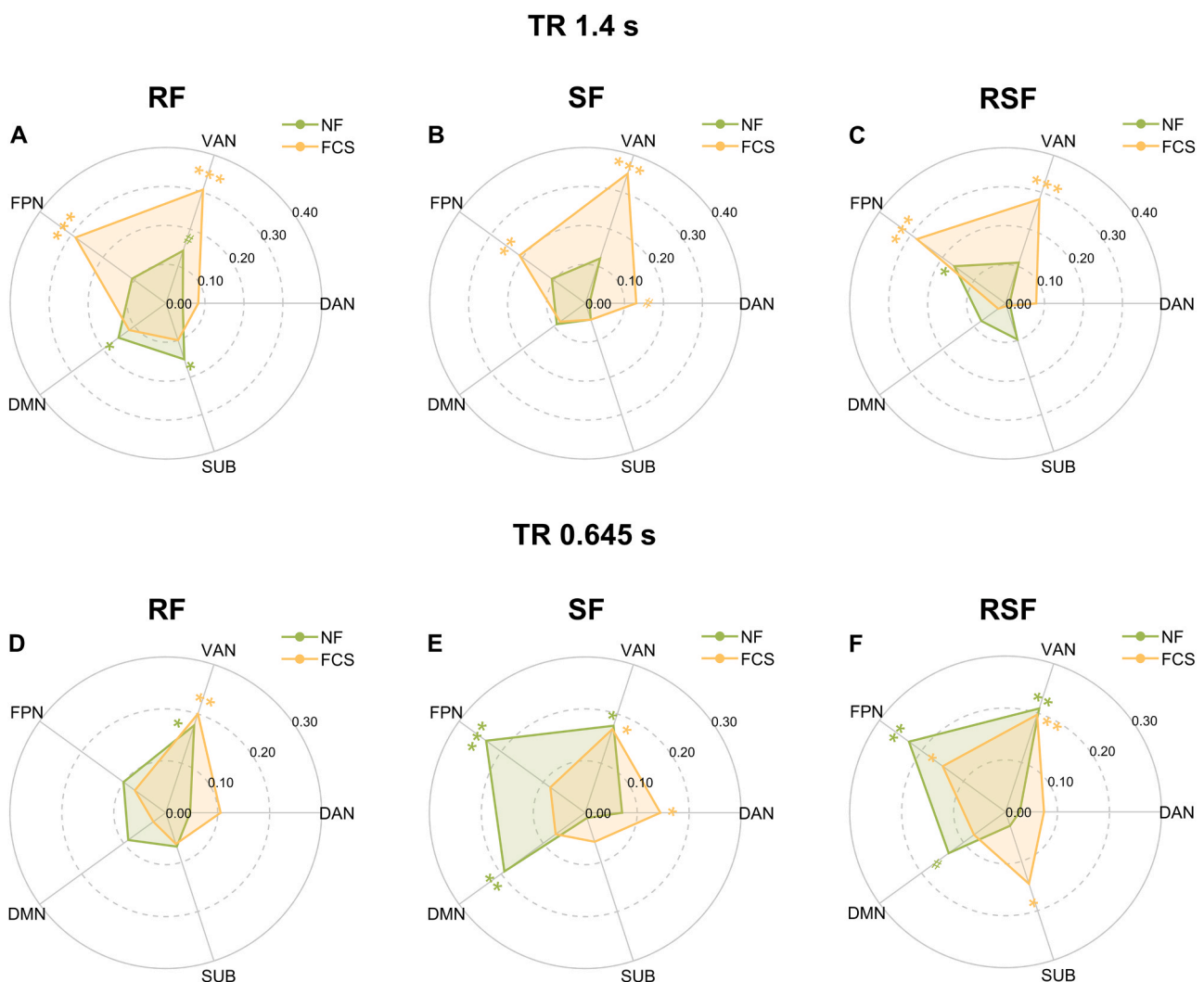
We calculated Pearson’s correlation coefficients to examine the similarities in behavioral outcomes between different tasks of the same or different types of flexibility. Using raw scores of single tasks, reactive flexibility and spontaneous flexibility showed higher within-type correlations (mean  $r = 0.51$ ,  $ps < 1.40 \times 10^{-7}$ ) than those of between-type (mean  $r = 0.42$ ,  $ps < 2.52 \times 10^{-7}$ , [Supplementary Tables S1 & S2](#)). The correlations between the two types substantially increased when using the SF and RF scores ( $r = 0.65$  and  $0.62$  for TR 1.4 s and TR 0.645 s datasets respectively,  $ps < 1.43 \times 10^{-22}$ ). These findings indicate a strong association between spontaneous and reactive flexibility, possibly reflecting the common mental processes involved in successful task implementation. Both SF and RF scores showed high correlations with the RSF score (both mean  $r = 0.69$  for each type,  $ps < 5.39 \times 10^{-28}$ ), implying that both types of flexibility contribute similarly to the tasks combining reactive and spontaneous flexibility.

Quadratic effects of age were consistently observed on the RF, SF,

and RSF scores (adjusted  $R^2 > 0.33$ ,  $ps < 1.36 \times 10^{-15}$ , [Fig. 2](#) and [Supplementary Table S3](#)) after controlling for sex and FIQ in both the TR 1.4 s and TR 0.645 s datasets. This suggests similar developmental trajectories for different types of cognitive flexibility, including high-speed growth in childhood, moderate-speed growth in adolescence, and a plateau in early adulthood.

#### 3.2. Development of functional brain networks

We found that the NF ( $0.43 < r < 0.69$ , all  $ps < 0.001$ ) and FCS ( $0.35 < r < 0.53$ , all  $ps < 0.001$ , [Supplementary Table S4](#)) showed a significant correlation between different TRs. For both the TR 1.4 s and TR 0.645 s datasets, the FCS of the VAN showed an inverted U-shaped relationship with age, while the NF of the VAN showed a U-shaped relationship with age (adjusted  $R^2 > 0.06$ ,  $ps < 0.003$ ). For both two datasets, the FCS of the FPN showed an increasing trend, whereas the NF of the FPN showed a U-shaped relationship with age (adjusted  $R^2 > 0.03$ ,  $ps < 0.05$ ). Furthermore, we discovered distinct age-related changes in FCS and NF: the FCS of the DAN linearly increased in the TR 1.4 s dataset (adjusted  $R^2 = 0.07$ ,  $p = 0.001$ ), the FCS of the SUB linearly decreased in



**Fig. 3.** Correlations between functional brain metrics and different types of cognitive flexibility. Absolute values of standardized  $\beta$  coefficients and the corresponding significance are shown. The upper panel illustrates the results of the TR 1.4 s dataset, and the lower panel illustrates the results of the TR 0.645 s dataset. The  $\beta$  coefficients between brain metrics and RF (A & D), SF (B & E), and RSF (C & F) scores. The green color indicates the NF and the yellow color indicates the FCS. RF: reactive flexibility; SF: spontaneous flexibility; RSF: reactive and spontaneous flexibility; DAN: dorsal attention network; VAN: salience/ventral attention network; FPN: fronto-parietal network; DMN: default mode network; SUB: subcortical network; FCS: functional connectivity strength; and NF: nodal flexibility; \*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ ; and #  $p < 0.1$ .

the TR 0.645 s dataset (adjusted  $R^2 = 0.08, p = 0.0002$ ), whereas the NF of the DMN showed a decreasing trend during development in both two datasets (adjusted  $R^2 > 0.03, ps < 0.049$ ) (Fig. 2D & 2H, Supplementary Table S5). Age-related changes in the FCS and NF were commonly observed in the VAN and FPN but were different in the DAN, SUB, and DMN.

3.3. Correlations between functional brain metrics and cognitive flexibility

We explored the direct correlations between functional brain metrics and cognitive flexibility. The VAN and FPN were reproducibly correlated with various types of cognitive flexibility across datasets and brain metrics ( $|\beta| > 0.14, ps < 0.06$ , Fig. 3, Supplementary Tables S6~S8). For the RF score, additional correlations were in the DMN and SUB in the TR 1.4 s dataset ( $|\beta| > 0.15, ps < 0.04$ , Fig. 3A, Supplementary Table S6). For the SF score, additional correlations were in the DAN in both datasets ( $|\beta| > 0.13, ps < 0.08$ , Fig. 3B & 3E, Supplementary Table S7) and in the DMN in the TR 0.645 s dataset ( $|\beta| = 0.19, p = 0.006$ , Fig. 3E, Supplementary Table S7). For the RSF score, additional correlations were in the DMN and SUB in the TR 0.645 s dataset ( $|\beta| > 0.14, ps < 0.06$ , Fig. 3F, Supplementary Table S8).

3.4. Mediating effects of functional brain networks on the development of cognitive flexibility

We tested the instantaneous mediating effects of age on cognitive flexibility through functional brain metrics controlling for sex and FIQ. The instantaneous mediating effects were examined at 11, 17, and 23 years old (-1 SD, mean, +1 SD of age). In the TR 1.4 s dataset, the FCS of the FPN mediated the relationships of age with the RF score (at age 11: instantaneous indirect effect  $[\theta] = 0.07, se = 0.05, 95\% \text{ CI} = [0.003, 0.19]$ ; at age 17:  $\theta = 0.04, se = 0.03, 95\% \text{ CI} = [0.003, 0.11]$ , Fig. 4A); the FCS of the VAN mediated the relationships of

age with the SF score (at age 11:  $\theta = 0.11, se = 0.06, 95\% \text{ CI} = [0.005, 0.26]$ ; at age 17:  $\theta = 0.06, se = 0.03, 95\% \text{ CI} = [0.001, 0.14]$ , Fig. 4B). In the TR 0.645 s dataset, the NF of the FPN mediated the relationships of age with the RSF score (at age 11:  $\theta = 0.05, se = 0.03, 95\% \text{ CI} = [0.008, 0.15]$ ; at age 17:  $\theta = 0.02, se = 0.02, 95\% \text{ CI} = [0.002, 0.06]$ , Fig. 4C) and with the SF score (at age 11:  $\theta = 0.06, se = 0.04, 95\% \text{ CI} = [0.005, 0.18]$ ; at age 17:  $\theta = 0.03, se = 0.02, 95\% \text{ CI} = [0.001, 0.08]$ , Fig. 4D); the NF of the DMN mediated the relationships of age with the SF score (at age 17:  $\theta = 0.02, se = 0.01, 95\% \text{ CI} = [0.0000, 0.06]$ , Fig. 4E). These results suggest that the FPN plays a common role in supporting the development of different types of cognitive flexibility, while the VAN and DMN may have unique contributions to the development of spontaneous flexibility.

Considering that the function of brain regions is largely determined by their connectivity profiles, we further examined the separate contributions of within- and between-network connectivity to the mediating effects. The FCS or NF of the FPN between-network connectivity mediated the association between age and the RF, SF, and RSF scores at 11 and 17 years old ( $\theta > 0.02$ , Supplementary Fig. S1A, 1D & 1E). The FCS of both within- and between-network connectivity of the VAN mediated the association between age and the SF score at 11 and 17 years old ( $\theta > 0.06$ , Supplementary Fig. S1B & 1C). The NF of the DMN between-network connectivity mediated the association between age and the SF score at 11, 17, and 23 years old ( $|\theta| > 0.03$ , Supplementary Fig. S1F). The NF of the DMN within-network connectivity mediated the association between age and the SF score at 11 and 23 years old ( $|\theta| > 0.05$ , Supplementary Fig. S1G).

3.5. Prediction of the enhancement of cognitive flexibility at the follow-up visit

Children and adolescents scored significantly higher on all types of cognitive flexibility at the follow-up than at the baseline ( $t > 2.63, ps < 0.01$ , Fig. 5A & 5E). Prediction models were built to examine whether

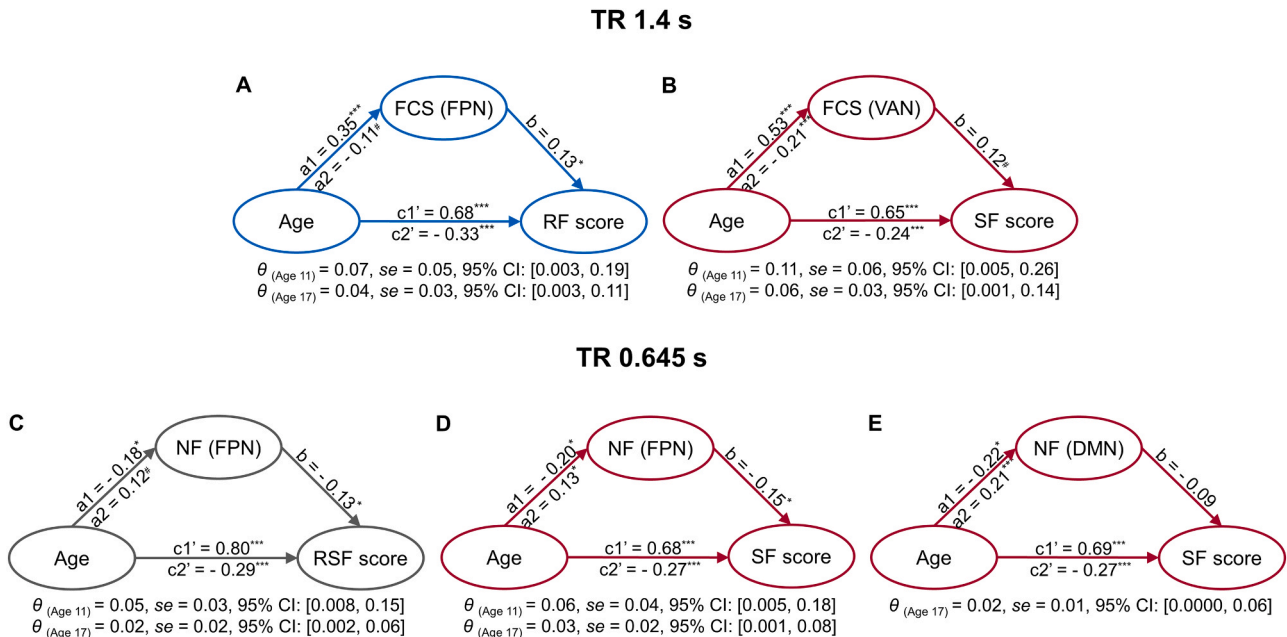
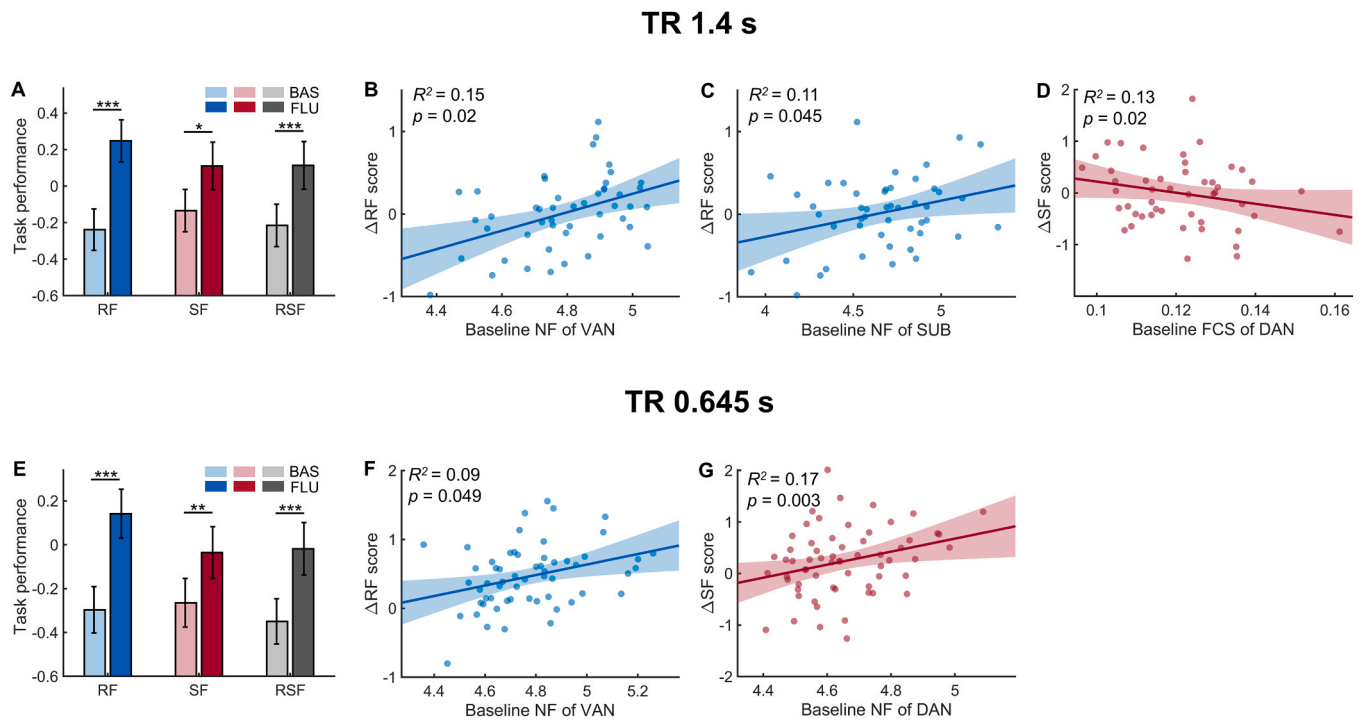


Fig. 4. Mediating effects of the functional brain metrics on the development of different types of cognitive flexibility. In the TR 1.4 s dataset, the FCS of the FPN mediated the development of RF (A), and the FCS of the VAN mediated the development of SF (B). In the TR 0.645 s dataset, the NF of the FPN mediated the development of RSF (C) and SF (D), and the NF of the DMN mediated the development of SF (E). a1: linear effects of age on brain metrics; a2: effects of age<sup>2</sup> on brain metrics; b: linear effects of brain metrics on cognitive flexibility; c1': direct linear effects of age on cognitive flexibility; c2': direct effects of age<sup>2</sup> on cognitive flexibility;  $\theta$ : Instantaneous indirect effects; CI: confidence interval. Standardized coefficients are shown. RF: reactive flexibility; SF: spontaneous flexibility; RSF: reactive and spontaneous flexibility; FCS: functional connectivity strength; NF: nodal flexibility; FPN: fronto-parietal network; VAN: salience/ventral attention network; DMN: default mode network; \*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ ; and #  $p < 0.1$ .





**Fig. 5.** Predictions of the increase in different types of cognitive flexibility 24–30 months later based on the brain metrics at baseline. In the TR 1.4 s dataset, (A) the RF, SF, and RSF scores are higher at the follow-up than at the baseline; the NF of the VAN (B) and SUB (C) at baseline predicts the increase in the RF scores; (D) the FCS of the DAN at baseline predicts the increase in the SF score. In the TR 0.645 s dataset, (E) the RF, SF, and RSF scores are higher at the follow-up than at the baseline; (F) the NF of the VAN at baseline predicts the increase in the RF scores; and (G) the NF of the DAN at baseline predicts the increase in the SF score. RF: reactive flexibility; SF: spontaneous flexibility; RSF: reactive and spontaneous flexibility; BAS: baseline; FLU: follow-up;  $R^2$ : adjusted R square;  $p$ : the original  $p$  of the regression model; 95 % confidence interval is highlighted in light color; VAN: salience/ventral attention network; SUB: subcortical network; DAN: dorsal attention network; NF: nodal flexibility; and \*\*\*  $p < 0.001$ .

the brain metrics at the baseline could predict the increment of cognitive flexibility at the follow-up after controlling for age and behavioral scores at the baseline. The NF of the VAN positively predicted the increment of the RF score in both TR 1.4 s and TR 0.645 s datasets (adjusted  $R^2 > 0.09$ ,  $p < 0.05$ , Fig. 5B & 5F), while the FCS and NF of the DAN predicted the increment of the SF score in both datasets (adjusted  $R^2 > 0.13$ ,  $p < 0.02$ , Fig. 5D & 5G). Additionally, the NF of the SUB positively predicted the increment of the RF score in the TR 1.4 s dataset (adjusted  $R^2 = 0.11$ ,  $p = 0.045$ , Fig. 5C). These findings suggest that the VAN plays a predictive role in the development of reactive flexibility, while the DAN plays a predictive role in the development of spontaneous flexibility.

### 3.6. Effects of sex on different types of cognitive flexibility and functional brain networks

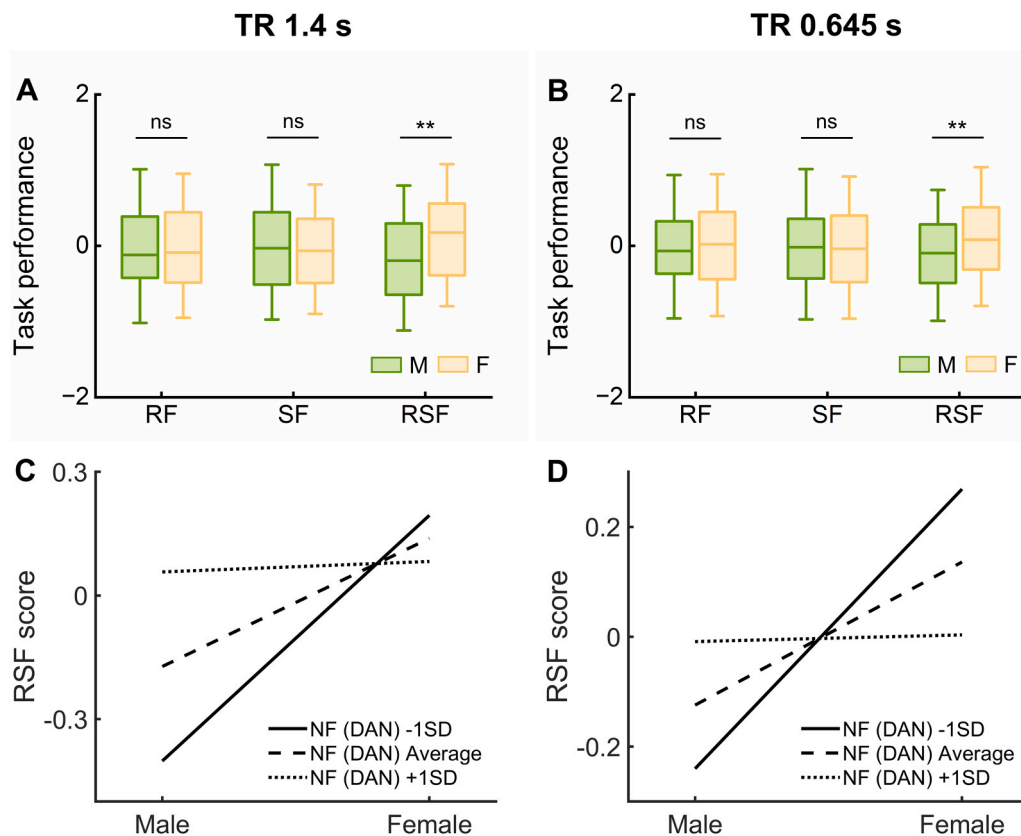
Further, we investigated the sex differences in cognitive flexibility and functional brain networks using general linear models. Significant sex effects were observed on the RSF score when we controlled for the linear and quadratic effects of age and FIQ in both the TR 1.4 s and TR 0.645 s datasets, and females showed higher RSF scores than males ( $t > 2.99$ ,  $ps < 0.003$ , Fig. 6A & 6B, Supplementary Table S3). No significant interactions were discovered between age or the square of age and sex ( $t < 0.51$ ,  $ps > 0.61$ ), indicating that sex differences in the RSF score may be introduced by the overall intercept but not the growth rate or turning point. No significant sex effect was observed on the RF or SF scores ( $|t| < 1.01$ ,  $ps > 0.32$ , Supplementary Table S3). This result indicates that the sex effect is manifested only in tasks measuring both reactive and spontaneous flexibility. No significant sex effect was observed in the FCS or NF of any network after controlling for age, FIQ, and head motion ( $t < 1.39$ ,  $ps > 0.17$ , Supplementary Table S5).

### 3.7. Moderating effects of functional brain networks on sex differences in RSF

We further explored the moderating role of brain metrics on sex differences in the RSF score, controlling for age and FIQ. We discovered that the NF of the DAN significantly moderated sex differences in the RSF score in both datasets ( $\beta < -0.25$ ,  $ps < 0.03$ , Fig. 6C & 6D). The sex difference was significant when the NF of the DAN was at a low level ( $-1$  SD,  $\beta > 0.51$ ,  $ps < 0.002$ ) and an average level ( $\beta > 0.26$ ,  $ps < 0.02$ ) but not at a high level ( $+1$  SD,  $\beta < 0.01$ ,  $ps > 0.94$ ). The increase in NF from the low to the average level improved the performance of tasks that combined reactive and spontaneous flexibility in males, whereas it was the opposite in females. This finding suggests that only the DAN plays a moderating role in sex differences in reactive and spontaneous flexibility.

### 3.8. Validation results

To examine the impact of WL in the sliding window technique when computing NF, we repeated the mediation, prediction, and moderation analyses using 30 s and 100 s as WL. In the TR 0.645 s dataset, the NF of the FPN mediated the relationship of age with the RSF and SF score at age 11 and 17 when WL = 30 s ( $\theta > 0.03$ , Supplementary Fig. S2A & 2B); We did not observe age-related changes in the NF of the FPN when WL = 100 s ( $|t| < 1.65$ ,  $ps > 0.10$ ), so the mediation analyses were not performed; The NF of the DMN mediated the relationship of age with the SF score at age 11 and 17 when WL = 30 s and 100 s ( $\theta > 0.02$ , Supplementary Fig. S2C & 2D). The NF of the VAN and SUB at baseline could predict the increment of the RF score, and the NF of the DAN at baseline could predict the increment of the SF score when WL = 30 s and 100 s (adjusted  $R^2 > 0.12$ ,  $ps < 0.03$ , Supplementary Fig. S3 & S4). The NF of the DAN moderated the sex difference in the RSF score when WL = 30 s



**Fig. 6.** Effects of sex on different types of cognitive flexibility. In both the TR 1.4 s and 0.645 s datasets, only the RSF score shows a sex effect, and females perform better than males (A & B). Median, 25 %, and 75 % percentiles, as well as SD are shown. The sex effect of the RSF score is moderated by the NF of the DAN (C & D). RF: reactive flexibility; SF: spontaneous flexibility; RSF: reactive and spontaneous flexibility; M: males; F: females; NF: nodal flexibility; DAN: dorsal attention network; \*\*  $p < 0.01$ ; and ns: not significant.

and 100 s in both datasets ( $\beta < -0.22$ ,  $ps < 0.06$ , [Supplementary Fig. S5](#)). These results suggest that our main findings are robust to the different window lengths.

We repeated the regression, mediation, and moderation analyses without controlling for FIQ. Specifically, we consistently observed an inverted-U-shaped relationship between age and various types of flexibility (adjusted  $R^2 > 0.26$ ,  $ps < 1.80 \times 10^{-13}$ , [Supplementary Fig. S6](#) and [Table S9](#)). Significant correlations were also observed between brain metrics of the VAN and FPN and different types of cognitive flexibility ( $|\beta| > 0.13$ ,  $ps < 0.10$ , [Supplementary Fig. S7](#) and [Tables S10~S12](#)). Moreover, the NF or FCS of the FPN significantly mediated the association between age and all types of flexibility scores, and the FCS of the VAN mediated the relationship between age and the SF score ( $\theta > 0.03$ , [Supplementary Fig. S8](#)). The NF of the DAN moderated the sex difference in the RSF score ( $\beta < -0.25$ ,  $ps < 0.05$ , [Supplementary Fig. S9](#)). These results suggest that our main findings are robust to controlling for FIQ.

In predictive analyses, we additionally predicted the follow-up scores using the baseline brain metrics, while controlling for the baseline age and scores. We found that the results were virtually identical to the main findings ( $ps < 0.04$ , [Supplementary Fig. S10](#)). Using the age-corrected behavioral scores, the baseline NF of the SUB and VAN could predict the follow-up RF score while the baseline NF of the DAN could predict the follow-up SF score after controlling for baseline scores ( $ps < 0.07$ , [Supplementary Fig. S11](#)). These findings suggest that the predictions of the SUB, VAN, and DAN may reflect the superior improvement.

#### 4. Discussion

This study aimed to investigate the convergence and divergence of reactive and spontaneous flexibility in the context of development. We used static and dynamic functional metrics and two datasets with different temporal resolutions to explore the neural basis of cognitive flexibility. We discovered that (1) the two types of cognitive flexibility showed similar quadratic effects of age, and their age-related changes during childhood and adolescence were mediated by the FPN, predominantly by the between-network connectivity of the FPN; (2) the NF of the VAN at the baseline visit could predict the increment of reactive flexibility during follow-up visits, while the FCS or NF of the DAN at baseline could predict the increment of spontaneous flexibility; and (3) females performed better than males on tasks that combined reactive and spontaneous flexibility, and the sex effect could be moderated by the NF of the DAN.

##### 4.1. FPN as the common network basis of different types of cognitive flexibility

We observed convergence in age effects between reactive and spontaneous flexibility, which was commonly mediated by the FCS or NF of the FPN. Specifically, both reactive and spontaneous flexibility were enhanced most in childhood and reached a plateau in early adulthood, which is in line with previous studies ([Cepeda et al., 2001](#); [Crone et al., 2004](#); [Hurks et al., 2010](#)). The FPN instantaneously mediated the development of different types of cognitive flexibility at the ages of 11 and 17 years in both datasets, further suggesting the crucial role of the FPN in cognitive flexibility in childhood and adolescence. The FPN is closely linked to a series of high-order cognitive abilities, such as

working memory, inhibition, and mental switch, which are commonly required in different types of cognitive flexibility (Menon, 2011). FPN is also recognized as the shared network basis of reactive and proactive control (Van Belle et al., 2014), which are the main processes in reactive and spontaneous flexibility respectively. Numerous studies have emphasized the importance of the FPN in supporting reactive flexibility through consistent activation and flexible connectivity patterns at different ages (Friedman and Robbins, 2022; Vallesi et al., 2022; Wendelken et al., 2012). Our study replicates the importance of the FPN in reactive flexibility development (Kupis and Uddin, 2023). Additionally, we provide evidence of the significance of the FPN in spontaneous flexibility, which corroborates the findings of behavioral and activation studies investigating this type of cognitive flexibility (Arán Filippetti and Krumm, 2020; Gurd et al., 2002; Hirshorn and Thompson-Schill, 2006; Kalkut et al., 2009). Taken together, our results reveal that FPN is the common network basis to support the development of different types of cognitive flexibility.

We further discovered that the mediating effect of the FPN on the development of different types of cognitive flexibility was dominated by between-network connectivity. The distributed connectivity pattern of the FPN allows effective information transfer to long-range regions and is a key indicator of brain maturation (Fair et al., 2009), supporting the development of various cognitive abilities in children (Chen et al., 2023; Kupis et al., 2021). We observed that the between-network connectivity of the FPN increased in the FCS and decreased in the NF during development. These age-related changes may be due to more stable connections between the FPN and other brain networks (Gu et al., 2015; Sanders et al., 2023). We speculate that the strengthening of between-network connections at rest may partially mirror the coactivation patterns of these regions under specific task conditions (Johnson, 2011; Smith et al., 2009). The coactivation and connectivity with other networks exert the FPN to engage in multiple cognitive tasks (Yeo et al., 2015) and to give rise to flexible behaviors (Cole et al., 2013).

#### 4.2. Unique network basis of different types of cognitive flexibility

We found unique networks (VAN and DMN) supporting the development of spontaneous flexibility but not that of reactive flexibility. Reactive flexibility was highly associated with functional metrics of the VAN (Fig. 3A & 3D), but the associations may be partially caused by the common factor of age since the associations disappeared when age was taken into account.

Therefore, the development of reactive flexibility mainly relies on the FPN. In contrast, spontaneous flexibility measures more cognitive abilities such as planning and memory retrieval and may need more neural supports. Spontaneous flexibility is more cognitively challenging than reactive flexibility with higher demands on working memory and inhibition to generate many but nonrepetitive answers (Arán Filippetti and Krumm, 2020). Regions in the VAN, for example, pre-supplementary motor area (pre-SMA), are considered to prepare expected cognitive demands which is important for proactive control and spontaneous flexibility (Burgess and Braver, 2010; Irlbacher et al., 2014). Another key region in the VAN, the temporoparietal junction (TPJ), can be triggered by internal memory-based stimuli and may be recruited in spontaneous flexibility tasks that are largely internally driven (Cabeza et al., 2012). The mediating effects of the VAN on the development of spontaneous flexibility may be associated with the key roles of VAN in proactive control and episodic memory retrieval. DMN is related to memory retrieval, preparatory control, and strategy shifts (Egan et al., 2024; Menon, 2023; Schuck et al., 2015). Spontaneous flexibility requires the recall from long-term knowledge especially for verbal tasks and various strategies to answer a question (Koren et al., 2005), which mainly rely on DMN and its between-network connectivity. Our findings reveal the unique roles of the VAN and DMN in the development of spontaneous flexibility.

#### 4.3. Predicting effects of attention networks on the improvement of different types of flexibility during development

In this study, we found predicting effects of VAN and DAN at baseline on the enhancement of reactive and spontaneous flexibility in follow-up visits, respectively. The prior mediation analyses revealed how cognitive flexibility develops through age-related changes in functional brain metrics, and the predictive analyses aimed to determine the neural biomarkers of the growth rate of cognitive flexibility. The predictive roles of the VAN and DAN were reliable in both datasets when using different time window parameters. Attention networks are sensitive to brain maturation (Atkinson and Braddick, 2012; Ciesielski et al., 2019; Onofrij et al., 2022) and individual differences in basic cognitive functions such as attentional reorienting, distractor filtering, and selective attention (Rohr et al., 2017; Vossel et al., 2014), which are potential mediators of the improvement of cognitive flexibility. Associations between the VAN and reactive flexibility have consistently been reported in adults and children, from brain activation to spatiotemporal dynamics (Chen et al., 2016; Kupis et al., 2021; Nomi et al., 2017; Taylor et al., 2012). Compared with spontaneous flexibility, reactive flexibility may require more in salience detection, attention shift, and rapid responses to errors, and these functions mainly depend on the VAN (Corbetta and Shulman, 2002; Ham et al., 2013; Uddin, 2015). In contrast, spontaneous flexibility demands higher in accessing various aspects of knowledge and a number of thoughts (Eslinger and Grattan, 1993), relying on the ability to maintain and reactivate internal representations, which are the functions of the DAN (Lückmann et al., 2014). Our findings suggest the unique importance of the VAN to reactive flexibility and the DAN to spontaneous flexibility.

#### 4.4. Moderating effects of the DAN on sex differences in RSF

We did not observe sex differences in either type of flexibility but in tasks that combined the two types of flexibility. These findings are in line with previous studies that used the same tasks and conditions (Arango-Lasprilla et al., 2017; Kalkut et al., 2009; Van der Elst et al., 2011; Welsh et al., 1991). The difference in RSF may imply that females have better performance on complex and cognitively challenging tasks that require a balance between different types of flexibility. Previous studies have reported the gender advantage for females in multitasking skills (Ren et al., 2009; Stoet et al., 2013), although it was not observed in other studies (Hirsch et al., 2019; Soldatova et al., 2019). Probably, the sex difference in RSF may be attributed to different paces of cognitive development that females develop earlier than males in certain fundamental abilities that are essentially crucial for complex cognitive control, such as verbal working memory (Voyer et al., 2021) and inhibition control (Silverman, 2021). Assessments combining different types of flexibility provide new insights into sex effects that cannot be uncovered by a single type of flexibility.

The NF of the DAN moderated the sex differences in tasks that combined reactive and spontaneous flexibility in both datasets. The results showed that a higher NF of the DAN may be linked with a better performance in males, whereas the opposite was true for females. During the performance of verbal fluency tasks, previous studies found that females switched more often between categories when generating words, whereas males tended to produce a larger cluster size (Scheuringer et al., 2017; Weiss et al., 2006). Moreover, males showed more frequent switches between brain states at rest (de Lacy et al., 2019), whereas females tended to spend more time in the states dominated by the DAN (Murray et al., 2021). Therefore, we speculate that the sex effect is likely due to the different cognitive strategies used in males and females when performing cognitive flexibility tasks, which may rely on distinct functional reconfigurations of the DAN.

#### 4.5. Methodological considerations

Brain metrics from both static and dynamic frameworks were used to characterize functional activity. These two metrics may reflect different aspects of brain activity, although there is some correlation between them (Yin et al., 2019; Zhang et al., 2016). Consistently, a decreasing trend of the DMN was observed only in the NF but not in the FCS during development. Interestingly, we discovered that the FCS of the FPN played a mediating role in the relationship between age and cognitive flexibility in the TR 1.4 s dataset, whereas the NF of the FPN played a mediating role in this relationship in the TR 0.645 s dataset. Moreover, the prediction effect of the SUB was only seen in the TR 1.4 s dataset but not in the TR 0.645 s dataset, which might be due to the relatively low signal-to-noise ratio for the SUB at short TR (Van Essen et al., 2013). Furthermore, we noticed that NF seemed to be more sensitive than FCS in the prediction and sex effect analyses. These findings further emphasize the importance of the selected approach for measuring spatiotemporal dynamics.

We used fMRI data with two different TRs. While the NF and FCS showed a significant correlation between the different TRs, the dynamic metric (NF) exhibited greater consistency. This suggests that different TRs yield similar patterns of brain connectivity. In addition, common functional networks were identified for age and sex effects across different TRs, indicating the reproducibility for the two TRs. Notably, we found that higher temporal resolution appears to lead to higher correlations between the dynamic metric and cognitive flexibility measures, while lower temporal resolution leads to higher correlations between the static metric and cognitive flexibility measures. Consistently, a prior study has also shown that brain dynamics obtained from the higher temporal resolution were more sensitive to age-related changes (Nomi, Bolt, et al., 2017). Despite the divergence, it should be noted that the common functional networks (i.e., FPN and VAN) were identified for different functional brain metrics at different sampling rates. Therefore, we suggest that the results found in different TRs can be explained by a common functional network basis and that sensitivities related to cognitive flexibility may differ across static and dynamic measures of different sampling rates. This may also suggest the importance of considering different functional brain metrics and sampling rates in future studies.

#### 4.6. Limitations

This study has some limitations. A previous study reported that longitudinal data were superior to cross-sectional data in detecting age-related changes in brain structure and function (Di Biase et al., 2023). However, the sample size of the longitudinal data available in this study was relatively small, so we were unable to further divide the participants into subgroups with a smaller age range. The inclusion of fMRI data with two different TRs may help test the reliability of the findings related to developmental changes over time. We consistently found that the NF of the VAN could predict the increment of reactive flexibility during development, while the FCS or NF of the DAN could predict the increment of spontaneous flexibility. This may indicate the reliability of the findings related to longitudinal data. Considering the lack of large and long-term follow-up longitudinal data, especially for functional images, we used mediation analysis for cross-sectional data according to previous studies (Baum et al., 2017; Satterthwaite et al., 2013). Notably, there is no temporal ordering in the mediation analysis with cross-sectional data. Therefore, the mediating effects should be interpreted with caution and need to be confirmed with a longitudinal study design.

Second, the same functional network partition was used for different age groups, potentially ignoring changes in network membership during development. However, both the static and dynamic metrics used in this study were calculated based on the (dynamic) functional connectivity profile of each brain region, without relying on any network partitions.

Instead, a fixed network partition was used only for the final statistical analysis of each metric, which was often employed in developmental studies (Betzel et al., 2014; Cui et al., 2020). This makes it easy to directly compare network-level measures between different age groups. Although fine-tuning reconfigurations of higher-order cognitive networks have been observed from childhood to adulthood (Gu et al., 2015; Oldham and Fornito, 2019), previous studies have also reported adult-like and stable functional architectures in children (Marek et al., 2015; Power et al., 2010). Therefore, the use of a fixed network partition for the summary purpose may not substantially affect the accuracy of identifying developmental changes in brain network dynamics.

Third, we did not include any measures of pubertal development. Recent studies have demonstrated the unique contributions of pubertal stages to the development of executive functions such as inhibition and attention (Chaku and Hoyt, 2019; Juraska and Willing, 2017; Ravindranath et al., 2022). It would be valuable for future studies to explore the relationship between pubertal development and cognitive flexibility and the underlying neural basis.

Finally, we used behavioral scores without controlling for basic cognitive functions related to the tasks. Cognitive flexibility has been successfully implemented with the coherent support of multiple cognitive processes. It is difficult to separate these basic functions from cognitive flexibility (Dajani and Uddin, 2015), and switching or shifting processes alone cannot represent cognitive flexibility (Cragg and Chevalier, 2012). Moreover, scores from multiple tasks were combined to reduce the negative impact of task specificity.

## 5. Conclusion

In summary, we demonstrated the common and unique network bases underlying the age and sex effects on reactive and spontaneous flexibility. The current study revealed a similar developmental trajectory and common neural basis for different types of flexibility in cognition, highlighting the crucial role of functional integration between the FPN and other networks in the development of cognitive flexibility. The VAN was uniquely correlated with reactive flexibility while the DAN was specifically important to spontaneous flexibility in predictions of behavioral improvement. The effect of sex was only observed in tasks that combined reactive and spontaneous flexibility and was moderated by the NF of the DAN, which further provided neural correlates for the sex effect. This study also highlights the importance of studying specific types of cognitive flexibility abnormalities in developmental neuropsychiatric disorders.

### CRediT authorship contribution statement

**Huang Ziyi:** Writing – original draft, Formal analysis, Conceptualization. **Yin Dazhi:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Author contributions

Z Huang and D Yin designed the research; Z Huang processed data and wrote the paper; D Yin revised the paper.

#### Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.dcn.2025.101528](https://doi.org/10.1016/j.dcn.2025.101528).

#### Data availability

All data used in this study were from the Enhanced Nathan Kline Institute Rockland Sample project ([https://fcon\\_1000.projects.nitrc.org/indi/enhanced/](https://fcon_1000.projects.nitrc.org/indi/enhanced/)).

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